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Incidence and clinical characteristics of second malignant neoplasms in children: a multicenter study of a polish pediatric leukemia/lymphoma group

Authors' Contribution:
A Study Design
B Data Collection
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G Funds Collection

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Summary

Background: The development of second malignant neoplasms (SMNs) in patients receiving chemotherapy and radiation therapy for primary cancers is one of the limitations to the quality and length of survival. The present study was undertaken to examine various characteristics of children who developed SMNs following successful therapy for primary leukemia or Hodgkin's disease (HD).

Material/Methods: A total of 3252 children with various forms of leukemia and 849 children with HD treated between, 1970–1997 at 7 pediatric centers of the Polish Pediatric Hematology/Oncology Group and subsequently followed-up entered the study. A second malignancy was diagnosed in 36 of these children.

Results: Of the 3252 patients diagnosed as having acute leukemia during this period, 16 developed SMNs (estimated frequency 0.49%). SMNs developed in 20 of the 849 children treated for HD (2.36%). The most frequent SMNs were soft tissue sarcoma and thyroid carcinomas, mainly following Hodgkin's disease. Other tumors occurred at about the same frequencies in both groups. The interval from the end of initial treatment to diagnosis of an SMN ranged from 2 years 7 months to 17 years 6 months, with a median of 7 yrs 4 mo. for acute lymphoblastic leukemia (ALL) patients and 10 years for children with HD. The estimated accumulated risk of SMN following acute leukemia is 0.95% at 15 years and, for HD, 5.1% at 20 yrs and 7% at 25 yrs.

Conclusions: Children who have been successfully treated for one cancer have a higher than expected incidence of additional tumors.

key words: **second malignant neoplasms • children • leukemia • lymphoma**

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BACKGROUND

Major advances in the treatment of childhood leukemia and other neoplasms have led to a significant improvement in survival. However, combined modality therapy, involving both chemotherapy and radiation therapy, also results in late side effects. One of the limitations to the quality and length of survival has been the development of second malignant neoplasms. Both radiation and chemotherapy have potential mutagenic and carcinogenic effects. A single radiation exposure is sufficient to increase the risk of cancer many years later. Many forms of chemotherapy have an effect on nucleic acid metabolism and are therefore potentially mutagenic. Alkylating agents are most frequently implicated in these chemotherapy-induced tumors [1–5].

The present study was undertaken to examine various characteristics of children who developed second malignant neoplasms (SMNs) following successful therapy for primary leukemia or Hodgkin's disease at 7 centers of the Polish Pediatric Leukemia/Lymphoma Group.

MATERIAL AND METHODS

A total of 3252 children with various forms of leukemia and 849 children treated for Hodgkin's disease entered the study. They had been treated between, 1970–1997 in 7 pediatric hematology/oncology centers of the Polish Pediatric Leukemia/Lymphoma Group and then a follow-up of each patient was performed at these centers. The information collected on each patient included sex, date of birth, family history of neoplasms and immune deficiencies, parents' occupations, and exposure to mutagenic agents. The description of the first malignant disease consisted of the date of diagnosis, histologic or cytologic diagnoses, clinical and hematologic features at diagnosis, and the type of chemotherapy and radiation therapy.

Details regarding second malignant tumors concerned the date of the second diagnosis, histologic examination, site, therapy and outcome. The estimated cumulative risk of SMNs was calculated according to the Kaplan-Meyer method. The at-risk time for a second malignancy began at the start of the first treatment with chemotherapy and ended on the date of diagnosis of the second neoplasm, the date of death, or the date of the most recent medical follow-up examination, whichever came first.

RESULTS

In the cohort of 4100 children with leukemia or Hodgkin's disease treated at our institutions, a second malignant tumor was diagnosed in 36 children. Primary malignancies in our patients had been diagnosed between, 1970 and, 1991. Of the total of 3252 children diagnosed with acute lymphoblastic leukemia (ALL) during this period, 16 developed SMNs. Their primary malignancy had been diagnosed at ages ranging from 2 years 8 months to 8 years 10 months (median 5.3 years). SMNs developed in 20 of the 849 children treated for Hodgkin's disease (HD), first diagnosed at ages ranging from 5 years to 11 years 4 months (median 7.19 years)

The second malignant tumors were disclosed in our patients between, 1977 and, 1997. Table 1 summarizes some of the clinical data of the 36 children who developed second tumors. A familial history of malignancies was not determined in any child with primary ALL. In 1 HD case, we obtained information concerning neoplastic diseases in family members which may suggest cancer susceptibility.

The distribution of second neoplasms in patients, divided into groups on the basis of type of the primary malignancy, is presented in the Table 2. The most frequent tumor was soft-tissue sarcoma, mainly following HD. Non-Hodgkin's lymphoma and neoplasms of the liver and central nervous system were observed in children treated for primary ALL.

The interval from the end of initial treatment to diagnosis of a second malignant neoplasm ranged from 2 yrs 7 mo. to 17 yrs 6 mo. with a median of 7 yrs 4 mo. for ALL patients and from 1 yr 11 mo. to 23 yrs. 7 mo. with a median of 10 yrs for HD patients.

Almost all patients had initially received both chemotherapy and radiation therapy. ALL children were treated according to protocols used at the time of diagnosis, i. e. BFM 81 or BFM 87, in all but four patients. Cranial irradiation was performed in all but one of these patients. In that child, astrocytoma developed as a secondary neoplasm. Chemotherapy of HD consisted of 6–8 cycles of the MVPP protocol in each case, 3 children receiving, in addition, courses of the B DOPA regimen protocol. All HD patients also received local radiation therapy.

Fourteen of our patients died of second neoplasms (8 ALL, 6 HD) and 20 children (63.8%) are still in remission (7 ALL, 13 HD). Information on 2 patients was not available.

The estimated cumulative risk for second malignant neoplasm in children with primary ALL was 0.05% at 5 years, 0.5% at 10 years, and 0.95% at 15 years (Figure 1). For patients with Hodgkin's disease the cumulative risk in our cohort was 0.02% at 5 years, 1% at 10 years, 3.5% at 15 years, 5% at 20 years, and 7% at 25 years (Figure 2).

DISCUSSION

It is now apparent that childhood cancer patients who have been successfully treated for one cancer have a higher than expected incidence of additional tumors [6]. The estimated risk of a child developing cancer in the first 15 years of life in the general Polish population is approximately 0.16% [7]. Thus, the cumulative risk for second malignant neoplasm following ALL in our study was 6 times higher than in the general population and 22 times higher for patients with HD.

Despite recent interest in second tumors, little is know about risk factors, in particular the influence of treat-

Table 1. Characteristics of patients with second malignant neoplasms.

No.	Sex	Age at primary dgx	Date of dgx (yr)	Primary neopl.	Age at SMN dgx	Interval	SMN	Outcome
1	F	5	81	ALL	13;11	8;11	NHL	UN
2	F	5;3	80	ALL	9;7	4;3	Hepatoblastoma	D
3	F	2;8	78	ALL	12;10	9;2	Ca hepatocholangiocellul	D
4	F	2;9	87	ALL	5;6	2;9	HD	CR
5	M	8;10	84	ALL	12;2	3;11	Astrocytoma	D
6	M	3;8	80	ALL	10	7;7	Synovioma malignum	CR
7	F	5;5	82	ALL	13	7;1	Ca gl. thyroid.	CR
8	M	8;7	87	ALL	9;1	6;1	Osteosarcoma	D
9	F	5;6	88	ALL	8;6	3	NHL	CR
10	F	10;9	91	ALL	13;6	2;7	Melanoma malignum	CR
11	M	6;3	80	ALL	21;4	15;1	Osteosarcoma	D
12	M	1;7	87	ALL	10;3	8;8	Renal cell ca	CR
13	F	1;10	87	ALL	8;10	7	Astrocytoma	D
14	F	2;11	85	ALL	12;1	9;2	B-NHL	D
15	F	8;6	80	ALL	26	17;6	Hepatoma	CR
16	F	2;7	89	ALL	7;10	5;3	Astrocytoma	D
17	M	6	74	HD	14;5	8;1	NHL	CR
18	F	15	83	HD	18;5	4;5	Fibrosarcoma	CR
19	F	11;4	74	HD	19	7;8	Fibrosarc.+ Leiomyosarc.	CR
20	M	7;8	73	HD	21;1	13;5	Chondrosarcoma	D
21	F	5;2	79	HD	6;9	1;11	Bronchoalveoral ca	D
22	M	3;4	81	HD	16	12;8	Ca gl. thyroid.	CR
23	M	4	85	HD	11;10	7;10	Ewing sa.	CR
24	F		81	HD		11;2	Adenoma foll. gl. thyroid.	CR
25	M	12;7	70	HD	34;5	21;10	Hepatocarcinoma	D
26	M	8	70	HD	15;5	7	Fibrosarcoma	UN
27	M	7;10	83	HD	17;10	10	Neurofibroma	CR
28	F	9;7	90	HD	13;6	4	NHL	CR
29	M	3;4	85	HD	14;1	10;9	Astrocytoma	CR
30	M	11;7	88	HD	19;8	8;1	Tu cerebri- PNET	CR
31	M	13	91	HD	16;6	3;6	NHL	D
32	M	7;10	83	HD	19;7	11;9	RMS	D
33	M	6;6	77	HD	25	18;6	Ca hepatis	D
34	F	10;10	71	HD	34;5	23;7	Ca basocell.	CR
35	F	9;10	89	HD	17;5	7;7	Ca gl. thyroid.	CR
36	M	7	87	HD	17;9	10;9	Ca gl. thyroid.	CR

Table 2. Distribution of first and second malignant neoplasms.

SMN (total)	Primary tumors	
	ALL (16)	HD (20)
Soft tissue sarc. (5)	1	4
NHL (6)	3	3
Liver neopl. (5)	3	2
Brain tu. (6)	3	3
Bone tu. (4)	2	2
Thyroid tu. (5)	1	4
HD (1)	1	–
Lung ca (1)	–	1
Other (3)	2	1

SMN – second malignant neoplasm; ALL – acute lymphoblastic leukemia; HD – Hodgkin's disease

ment of the first primary neoplasm on the development of a second. Two cause are most likely: the induction of second tumors by treatment with mutagenic and carcinogenic agents, and the survival of a group of patients with increased susceptibility to cancer. Whether treatment is a direct or indirect cause of SMN or whether the prolonged survival induced by such treatment allows for the development of SMN in a genetically susceptible subject cannot be answered with certainty. Most studies implicate X-radiation as the causative agent, but there is now evidence that patients treated with chemotherapy, especially with alkylating agents, also have an increased risk of second primary tumors, and those treated with both X-ray and chemotherapy have the highest incidence of all [1,3,5,8,9].

SMN incidence, or the cumulative risk of SMN, in patients previously treated for primary cancer differs in the groups studied [1–5,10–21]. Since different cure rates have to be considered throughout the years, 1959–1990, the incidence of second malignancies cannot be directly related to the total number of patients, but only to the percentage of long-term survivors, which was less than 20% for patients with leukemia in the years, 1950–1970 and more than 60% in, 1980–1990 [22].

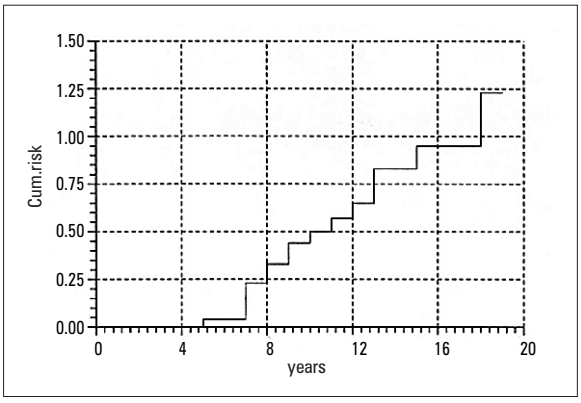

Figure 1. Cumulative risk for SMN in children with acute lymphoblastic leukemia.

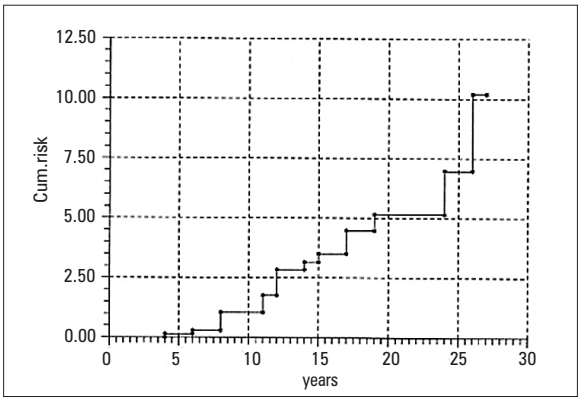

Figure 2. Cumulative risk for SMN in children with Hodgkin disease.

Few studies have attempted to describe the overall risk of a second neoplasm among children with ALL. In the 4373 children with leukemia studied by the Late Effect Study Group, only 5 (0.11%) developed SMN [10]. Pui et al. [3] studied the risk of the development of AML in 733 children with a primary diagnosis of ALL and treated with intensive chemotherapy. The cumulative risk was 1.6% at 3 years, and 4.7% at 6 years. In another study, 3% of 95 ALL patients developed SMN [11]. Neglia et al. [12] found an SMN incidence of 0.44% in 9720 children who had been diagnosed with ALL. In more recent studies from Nordic countries [13], the cumulative risk of SMN in patients treated for primary leukemia, based on a cohort of 981 children, was 2.9% at 20 years. The Italian Group [14] reported a study within a cohort that included 1806 patients with leukemia and they found that the cumulative risk was 0.1% at 5 years 2.6% at 10 years, and 4.5% at 15 years. A cohort of 8831 children diagnosed with ALL and enrolled in Children's Cancer Group therapeutic protocols between, 1983 and, 1995 were observed to determine the incidence of second neoplasms and associated risk factors. Sixty-three patients developed second neoplasms. The cumulative incidence of any second neoplasm was 1.18% at 10 years, representing a 7.2-fold increased risk compared with the general population [15]. The BFM Group presented a study of 5006 children with B-precursor or T-ALL who were enrolled in 5 ALL-BFM multicenter trials. A total of 52 second malignancies were documented in these group [16]. Compared with the expected numbers estimated from incidence rates, this represented a 14-fold increase for all cancers, and the overall cumulative risk of SMN at 15 years was 3.3%.

These figures are higher than the results estimated in our study, i.e. 0.05%, 0.5%, and 0.90%, respectively. The number of children with ALL at follow-up (3252) in our study was, however, comparable to that in other studies.

The frequency of SMN has been extensively investigated in patients successfully treated for Hodgkin's disease (HD). Tester et al. [4] reported actuarial estimates of the risk of AML and secondary solid tumors for patients treated for HD. The risk of developing AML 10 years after diagnosis was 6±4.5% among patients treated with MOPP + radiation therapy. The actuarial risk of developing a solid SMN was 7±2.6% among those treated with radiation therapy only, and 7±4% among those treated with initial combined-modality therapy. In another group of 441 patients with HD treated with a MOPP regimen, SMN developed in 2.27%, and the actuarial risk at 15 years was 3.5% [23]. The Late Effects Study Group reported on 1380 children with HD and 88 SMN were diagnosed (expected: 4.4). The estimated actuarial incidence of SMN 15 years after diagnosis of HD was 7% [17]. This is in good agreement with results presented by Beaty [18]. The cumulative risk estimated in Nordic countries was 1.9% at 10 years, 6.9% at 20 years, and 18% at 30 years [19]. Higher risks were estimated in, 1939 Dutch patients, with 20% at 20 years [20], and in a cohort reported by Green et al. [24], with 26.27±6.75% at 30 years after diagnosis. Lower, however, cumulative risk was reported in a cohort of Italian patients, with 0.8% at 5 years, 1.6% at 10 years, and 4.1% at 15 years (14).

The risk of second cancers estimated in our cohort of children with HD 15 years after diagnosis (3.5%) is close to the last value and lower than that presented in most other papers. Schellong et al. [21] recently reported on a group of 667 children with HD and estimated the risk even smaller than in our study (1.1% at 15 years).

The median interval from initial therapy to the development of secondary acute leukemia was reported to be from 23 months to 110 months [14,17], i. e. from less than 2 years to almost 10 years. In most studies, however, the median time between the beginning of treatment of the primary tumor and the diagnosis of the second acute leukemia was 36 months [3], 48 months [8], 57 months [25], 60 months [26,27], and 94 months [28]. In all studies, the latent period for second leukemia ranged from 11 months to 17 years. In patients treated previously for HD, the latent period seemed to be similar to that observed in patients with primary leukemia, i. e. about 6 years in most studies [2,29] and 4.2 years in the cohort reported by Lavay [1].

SMN in our patients developed after a latent interval ranging from 31 months to 17 years 4 mo. (median: 7

years 4 mo.) for ALL patients and from 13 months to 23 years 7 months for HD patients. This time between the diagnosis of primary cancer and a second neoplasm is in good agreement with most other reports. In patients treated for lung cancer, SMN also developed after a mean time of 50.6 months [30]. In another group of patients with different primary neoplasms, SMN was observed after a mean time of 5 years, but the latent period was longer (10 years) for patients whose SMN developed after radiotherapy [9]. Whitlock et al. [5] stated that the latency period for etoposide-related or teniposide-related ANLL is significantly shorter than that for ANLL occurring secondary to alkylating agents. The mean interval from exposure to an epipodophyllotoxin to the onset of leukemia is 33 months, in contrast to a mean interval of 58 to 73 months for alkylating agent-associated or radiation-associated leukemia.

The incidence of SMN is time dependent and the median follow-up period of patients seems to play an important role [2]. The risk increases significantly between 5–10 years from the first tumor diagnosis and gradually reduces a level of the expected outcome thereafter [1,5,6,31].

The diagnosis of a second malignancy in children shortly after the diagnosis of a primary cancer might indicate that cases of relapse or metastases were concealed among the group designated as second primaries [6]. Currently, a proper diagnosis is much more likely using immunologic and cytogenetic methods and new imaging techniques. The occurrence of a second cancer in a child may depend on factors other than previous therapy: it may also be a result of a combination of age, genetics and, possibly, therapy (2, 12). Genetic predisposition is thought to play a special role in the development of SMN. Well-defined cytogenetic abnormalities have been reported for secondary leukemias [5,8,25,28–34).

The clinical outcome of treatment in our patients with SMN seems to be better than in previous reports [3]. At least 50% of the 36 children in our study are still in a second complete remission with the shortest follow-up period of 2 years.

As survival continues to improve, second cancers and other late effects of therapy will play an increasingly prominent part in the long-term care of children with cancer. It is not certain, however, whether the intensity of the treatment presently being administered is needed to achieve cure. An optimal balance between the risks and benefits of treatment must be applied.

CONCLUSIONS

Childhood patients who have been successfully treated for one cancer have a higher than expected incidence of additional tumors. The cumulative risk for second malignant neoplasm following ALL in our study was 6 times higher than in the general population and 22 times higher for patients with HD. The SMNs in our patients developed after a median latency interval of 7 years 4 mo. for ALL patients and 10 years for HD patients.

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